CASE REPORT

# Neuroleptic Malignant Syndrome After the Use of Venlafaxine in a Patient with Generalized Anxiety Disorder

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Neuroleptic malignant syndrome (NMS) is a potentially lethal adverse reaction to neuroleptics, which is characterized by hyperthermia, extrapyramidal symptoms, altered consciousness and autonomic dysfunction. Although NMS is most commonly induced by the high-potency neuroleptics, its development has also been associated with the use of non-neuroleptic agents that block central dopamine pathways. A 68-year-old man with generalized anxiety disorder and depressive symptoms presented at the emergency department (ED) with high fever, tremor, muscle rigidity, rhabdomyolysis and altered mental status. NMS was considered to have been caused by the recent addition and subsequent dose increase in his treatment regimen of venlafaxine, a serotonin norepinephrine reuptake inhibitor. He was successfully treated with bromocriptine, lorazepam, and fluid hydration in the ED and intensive care unit. [*J Formos Med Assoc* 2006;105(1):90–93]

**Key Words:** neuroleptic malignant syndrome, venlafaxine

Neuroleptic malignant syndrome (NMS) is a rare complication of treatment with neuroleptic drugs. Few cases of NMS have been reported to be caused by use of selective serotonin reuptake inhibitor (SSRI) or serotonin norepinephrine reuptake inhibitor (SNRI).[1–3] We report a 68-year-old man with generalized anxiety disorder who developed acute onset of hyperthermia, altered mental status, rigidity, tremor and rhabdomyolysis 9 days after treatment with venlafaxine, a dual SNRI. The clinical symptoms of NMS are described, in close relation to the initiation of new treatment with venlafaxine. The possible pathologic mechanism of NMS in this patient is discussed.

## Case Report

A 68-year-old man was sent to the emergency room after suddenly developing symptoms of high fever, tremor and altered mental status. A DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) axis I diagnosis of generalized anxiety disorder with depressive symptoms not fulfilling the criteria of major depression was first made 6 years prior to admission. He had been treated with propranolol, buspirone, clonazepam, trazodone and fluoxetine. In the 2 months prior to admission, his depressive symptoms had exacerbated and he had involuntary movements of four limbs and difficulty in initiating walking. On a visit to the psychiatric outpatient clinic 9 days prior to this admission, amantadine 50 mg three times daily was added under the tentative impression of Parkinsonism, and fluoxetine was changed to venlafaxine 75 mg once daily. One week later, amantadine and venlafaxine doses were increased to 100 mg and 75 mg twice daily, respectively.



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Initial assessment on arrival at the emergency department revealed that the patient was obtunded and disorientated. His body temperature was 39.7° C, pulse rate was 142 bpm, respiratory rate was 30/min, and blood pressure was 162/92 mmHg. Neurologic examination showed mild neck stiffness without meningism, normal deep tendon reflexes, extreme limb tremors, and cogwheel rigidity.

Biochemical measures were normal except for increased serum creatine kinase (CK) (1122 U/L; normal, 38–160 U/L), aspartate transaminase (58 U/L; normal, 5–31 U/L) and alanine transaminase (69 U/L; normal 0–41 U/L) levels. White blood cell (WBC) count was $6.27 \times 10^9$/L with 90.4% neutrophils. Brain computed tomography revealed no abnormalities. Lumbar puncture showed normal intracranial pressure (opening pressure, 120 $mmH_2O$; closing pressure, 85 $mmH_2O$) without the presence of pleocytosis.

His temperature elevated to 41.5° C despite receiving fluid hydration (0.9% sodium chloride) and antipyretics with oral acetaminophen 500 mg, intramuscular ketorolac 30 mg, and intravenous lysine acetylsalicylate 0.9 g. NMS was diagnosed and the suspected offending drug, venlafaxine, was discontinued. Bromocriptine 2.5 mg twice a day was given. Amantadine and other anxiolytics and antidepressants were maintained after neurologic and psychiatric consultations. Severe limb tremors and muscle rigidity were noticed and showed dramatic response to intravenous administration of lorazepam 2 mg. He was then admitted to the intensive care unit (ICU) for further care.

After ICU admission, fluid hydration, urine alkalization, and other supportive treatments were given. CK level was 25,934 U/L and WBC count was $12.25 \times 10^9$/L with 88.0% neutrophils on the next day, but these elevated laboratory values declined thereafter. Tremors and rigidity improved after admission. The septic workup yielded negative results. He was afebrile 3 days later and his level of consciousness returned to his previous condition. He was then transferred to a regular medical ward and was free of symptoms at discharge 12 days later.

## Discussion

NMS, which is thought to be an idiosyncratic drug reaction, is a rare but potentially lethal complication of treatment with neuroleptics. According to one theory, decreased dopamine activity in the central nervous system (CNS), either from blockade of dopamine D2-receptors or decreased availability of dopamine itself, plays a role in the pathogenesis of NMS.[4] Manifestations of NMS may include autonomic instability, hyperpyrexia, altered mental status, and extrapyramidal reactions.[5] The appearance of these symptoms, especially extrapyramidal reactions in patients receiving antipsychotic drugs, should alert physicians to include NMS in the differential diagnosis. Although extrapyramidal reactions or NMS are most likely to be associated with the use of high-potency neuroleptics, these uncommon side effects have been reported to be associated with SSRI use.[1,2] Serotonin's inhibitory action on SSRI-induced extrapyramidal dopamine activity has been proposed to contribute to the etiology.[6] Some authors have also hypothesized that individuals who develop extrapyramidal symptoms after SSRI use may actually have preclinical Parkinsonism.[7,8]

Venlafaxine is an SNRI. There have been an increasing number of reports of extrapyramidal reactions in association with venlafaxine.[9–11] It has been reported to induce NMS when combined with trifluoperazine.[3] Cassidy and O'Kearne considered that absence of altered sensorium and a relatively benign course, as in the above-reported patient, are more likely to be serotonin syndrome than NMS.[12]

NMS and serotonin syndrome are difficult to differentiate because of their overlapping clinical features. The diagnostic criteria for serotonin syndrome as proposed by Sternbach are: recent change of a potent serotonin agent; no history of substance abuse or infectious or metabolic disease; absence of treatment with any antipsychotic drug; and ≥ 3 of the following symptoms: (1) change in the finding of the mental status, (2) agitation, (3) myoclonus, (4) hyperreflexia,

(5) diaphoresis, (6) shivering, (7) tremor, (8) diarrhea, (9) uncoordination, and (10) fever.[13] Serotonin syndrome has been reported to be induced by the use of venlafaxine in combination with monoamine oxidase inhibitors such as tranylcypromine or phenelzine.[14–16] Isolated and even low-dose venlafaxine-induced serotonin syndrome has been reported.[17,18] Although serotonin syndrome has been increasingly recognized as a possible adverse event in patients who receive SNRIs like venlafaxine, it is also possible that NMS may occur through their serotonergic inhibition of central dopaminergic activity, a mechanism similar to extrapyramidal adverse drug reactions.

The differential diagnosis of NMS should include malignant hyperthermia (MH), which is another important cause of drug-induced fever. Although both MH and NMS are characterized by hyperthermia, rhabdomyolysis, tachypnea, consciousness disturbances, and acute renal failure, MH is now referred to as a genetic disease of the skeletal muscle triggered on exposure to volatile anesthetic agents or depolarizing muscle relaxants.[19]

Our patient shared many overlapping features of drug-induced fever like serotonin syndrome and MH, but he did not receive any volatile anesthetics or succinylcholine, and the relatively gradual onset and severe clinical manifestations favored a diagnosis of NMS rather than serotonin syndrome. Based on these considerations, the patient was diagnosed with NMS rather than other drug-induced fever due to the presence of extrapyramidal symptoms with severe rigidity, severe hyperthermia, rhabdomyolysis with elevated CK, leukocytosis with abnormal liver function, and altered mental status.

There are some diagnostic "weak points" in the implication of NMS. The lack of uniformly accepted diagnostic criteria makes the diagnosis of drug-induced NMS more difficult.[20] Such diagnosis of drug-induced fever can only be established by withdrawal of the drug and subsequent rechallenge, which would be an unethical practice. Further study is needed to accurately and precisely assess the risk of adverse drug reactions and drug-drug interactions with novel antidepressants.

In summary, the use of venlafaxine may be implicated in the development of NMS in patients with clinical manifestations of Parkinsonism, possibly due to its serotonergic inhibition of the central dopaminergic system. Greater awareness of this potential side effect may facilitate early recognition and treatment to decrease its morbidity.

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